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Abstract

Objective: To study alcohol consumption in relation to ovarian cancer risk in a prospective cohort study.
Methods: The Netherlands Cohort Study on diet and cancer was initiated in 1986. A self-administered questionnaire on dietary habits and other risk factors for cancer was completed by 62,573 postmenopausal women. Follow-up for cancer was established by annual record linkages with the Netherlands Cancer Registry. After 9.3 years of follow-up, 214 incident invasive epithelial ovarian cancer cases and 2211 subcohort members with complete data on alcohol intake were available for analysis. All incidence rate ratios (RRs) were corrected for age, use of oral contraceptives, parity, height, body mass index, energy intake and current cigarette smoking.
Results: The RRs of ovarian cancer for women who consumed up to 5, 15 and >15 g of alcohol per day were 1.13 (95% confidence interval, 95% CI = 0.79–1.63), 0.85 (95% CI = 0.53–1.37) and 0.92 (95% CI = 0.55–1.54), respectively, compared to non-drinkers. Alcohol consumption in the form of wine, beer or liquor was not associated with ovarian cancer risk.
Conclusion: These data do not suggest a major association between alcohol intake and ovarian cancer risk in this population.

Introduction

In 1988, the International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of alcohol in humans [1]. Although experimental studies have not shown a carcinogenic effect of ethanol as such, the epidemiological data with respect to several cancers are strong [1, 2].

The effect of alcohol on the risk of ovarian cancer may, however, be different. Alcohol may have an enhancing effect, as it has in other sites, but it could also have a protective effect [3]. In premenopausal women, alcohol intake has been associated with reduced serum levels of gonadotropins [4]. Also, alcohol-fed rats developed significant ovarian atrophy, showing an absence of corpora lutea and developing follicles [5]. Based on these observations, two of the hypotheses for the etiology of ovarian cancer – the 'incessant ovulation' theory of Fathalla [6] and the 'excessive gonadotropin' hypothesis of Cramer and Welch [7] – predict a protective effect of alcohol intake on the risk of ovarian cancer.

The results of published epidemiological studies investigating the association between alcohol consumption and ovarian cancer have been heterogeneous, however. Most case–control studies, often hospital-based, did not find a statistically significant association [8–16]. Two case–control studies reported statistically significantly decreased risks [17, 18], whereas two other case–control studies reported increased risks [19, 20]. To date, only two cohort studies have been conducted. A cohort study with 76 cases among alcoholic women in Sweden [21] showed that the incidence of ovarian cancer was decreased among women under 60 years relative to the general population. Among women of 60 years and

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older, however, there was no association. The second cohort study, with 139 cases, was conducted in Iowa, and found a significantly decreased risk of ovarian cancer [22]. Of the prospective cohort studies, only one adjusted for confounders. We therefore decided to study alcohol consumption in relation to ovarian cancer in a prospective cohort study, allowing adjustment for the main potential confounders.

Materials and methods

The cohort

The Netherlands Cohort Study on diet and cancer (NLCS) started in September 1986, when 62,573 Dutch women aged 55–69 years were enrolled in the cohort [23]. All women were presumed to be postmenopausal. Data processing and analysis were based on the case–cohort approach, in which the cases were enumerated for the entire cohort (numerator information on incidence rates), while the accumulated person-years of the entire cohort were estimated using a subcohort sample (providing the denominator information). Following this approach, a subcohort of 2589 women was sampled randomly from the cohort after the baseline exposure measurement. The design of the study has been described in detail before [23]. One hundred and forty-five prevalent cancer cases (other than skin cancer) were excluded from the subcohort. In addition, women in the subcohort who had reported at baseline to have undergone an oophorectomy (n = 32) were excluded, leaving 2412 subcohort members.

Follow-up

The subcohort has been followed up biennially by mail for vital status information. The vital status of subcohort members who did not respond to the letter was completed by contacting the municipal register. Incident cancer cases occurring in the entire cohort were identified by record linkage to the Netherlands Cancer Registry and the Netherlands National Database for Pathology (PALGA) [23, 24].

The present analysis is restricted to cancer incidence in the 9.3-year follow-up period from September 1986 to December 1995. The completeness of cancer follow-up was estimated to be at least 96% [25], and no subcohort members were lost to follow-up. During a follow-up period of 9.3 years, 256 incident, microscopically confirmed, primary ovarian malignancies were detected. After exclusion of non-epithelial tumors (n = 15) and borderline invasive tumors (n = 6), 235 cases with epithelial ovarian cancer remained available.

Questionnaire data

At baseline, cohort members completed a self-administered questionnaire on risk factors for cancer. The food-frequency section concentrated on habitual consumption during the preceding year. Consumption of alcoholic beverages was addressed by questions on beer, red wine, white wine, sherry, other fortified wines, liqueur, and liquor. The questionnaire data of all cases and subcohort members were key-entered twice and processed in a manner blinded with respect to case/subcohort status in order to minimize observer bias in the coding and interpretation of data. The questionnaire has been validated against a nine-day diet record [26, 27]. The Pearson correlation coefficient between the mean daily ethanol intake assessed by the questionnaire and that estimated by the 9-day record was 0.86 for all subjects and 0.78 for users of alcoholic beverages [26]. Respondents who drank alcoholic beverages less than once a month were considered non-drinkers. Four items from the questionnaire (*i.e.*, red wine, white wine, sherry, and liqueur) were combined into one wine variable, since these items were substantially correlated and separate treatment would have resulted in a sparsity of data. Mean daily alcohol consumption was calculated using the Dutch food composition table [28]. On the basis of pilot study data, standard glass sizes were defined as 200 ml for beer, 105 ml for wine, 80 ml for sherry, and 45 ml for both liqueur and liquor, corresponding to 8, 10, 11, 7, and 13 g of alcohol, respectively.

Data analysis

The analysis was based on 214 cases and 2211 subcohort members for whom data on alcohol consumption were complete. Of the 214 epithelial ovarian carcinomas, 35.5% were serous carcinomas, 10.7% endometrioid carcinomas, 10.7% mucinous carcinomas, 4.7% clear cell carcinomas, 35.5% adenocarcinomas not otherwise specified and 2.8% other carcinomas.

The following variables were considered as potential confounders [3, 29, 30]: age (years); use of oral contraceptives (ever *versus* never); parity (number of children); use of postmenopausal hormones (ever *versus* never); height (cm); body mass index (kg/m^2); family history of breast and/or ovarian cancer (yes *versus* no); hysterectomy (yes *versus* no); total energy intake (including energy intake from alcoholic drinks; kcal/day); and current cigarette smoking (yes *versus* no). Family history was considered positive if breast and/or ovarian cancer was reported in at least one first-degree relative, *i.e.*, mother, sister or daughter. A variable was considered a confounder if (1) the variable was statistically signifi-

Table 1. Means (standard deviation) and distribution of potential confounders in the subcohort according to alcohol consumption, the Netherlands Cohort Study, 1986–1995

Characteristic		Alcohol consumption			
		No (n = 726) Mean (SD[a])	0.1–4 g/day (n = 791) Mean (SD[a])	5–14 g/day (n = 408) Mean (SD[a])	≥15 g/day (n = 286) Mean (SD[a])
Age at baseline	Years	61.7 (4.3)	61.4 (4.3)	61.5 (4.2)	60.8 (4.2)
Parity	no. of children	3.0 (2.4)	2.8 (2.3)	2.7 (2.0)	2.6 (2.0)
Height	cm	164.8 (6.7)	165.3 (6.1)	165.2 (5.9)	166.0 (5.8)
Body mass index	kg/m^2	25.5 (3.9)	25.2 (3.4)	24.5 (3.2)	24.4 (3.2)
Energy intake	kcal	1617 (425)	1674 (382)	1724 (387)	1793 (411)
		%	%	%	%
Use of oral contraceptives	Yes	21.0	22.9	30.3	33.7
Use of postmenopausal hormonal therapy	Yes	10.8	11.8	14.8	15.4
Hysterectomy	Yes	5.4	5.2	9.6	8.0
Family history of breast/ovarian cancer[b]	Yes	9.6	9.5	7.1	8.0
Currently smoking cigarettes	Yes	18.9	16.6	26.0	38.1

[a] SD, standard deviation.
[b] Family history was considered positive if breast and/or ovarian cancer was reported in at least one first-degree relative, *i.e.* mother, sister or daughter.

cantly associated with alcohol consumption; (2) the variable is known to be a risk factor for ovarian cancer in this population and (3) the association of alcohol consumption with the risk of ovarian cancer changed by more than 10% after adjustment for the variable. Cases and subcohort members were excluded from multivariate analyses if information on confounders was missing.

Incidence rate ratios (RR) and corresponding 95% confidence intervals (CI) for ovarian cancer were estimated in the age-adjusted and multivariate case–cohort analyses with categorized and continuous alcohol variables, using the Cox proportional hazards model [31] processed with the Stata statistical software package [32]. Standard errors were estimated using the robust Hubert–White sandwich estimator to account for additional variance introduced by sampling from the cohort. This method is equivalent to the variance–covariance estimator presented by Barlow [33]. The proportional hazards assumption was tested using the scaled Schoenfeld residuals [34]. Tests for dose–response trends in risk of ovarian cancer were assessed by fitting ordinal exposure variables as continuous terms. Two-sided *p*-values are reported throughout the paper.

Results

Among subcohort members, women who drank alcohol were slightly younger, had fewer children on average, were taller and leaner and had a higher energy intake than non-drinkers (see Table 1). Of the women who drank alcohol, more had ever used oral contraceptives or postmenopausal hormonal therapy, and more were current cigarette smokers. Because age, use of oral contraceptives, parity, height, body mass index, energy intake and current smoking changed the risk estimates for the association of alcohol consumption with the risk of ovarian cancer, these variables were included as confounders in the multivariate analyses. After exclusion of cases and subcohort members with incomplete information on confounders, 180 cases and 2005 subcohort members were available for multivariate analysis.

The consumption patterns among the women were quite stable. Only 4.7% of the cohort members and 2.8% of the cases who consumed less than one alcoholic drink per month at baseline reported to have used alcoholic drinks five years before baseline.

Women who drank 15 g of alcohol or more per day had a multivariate adjusted relative risk (RR) of 0.92 (95% CI = 0.55–1.54) compared to women who did not drink alcohol (Table 2). The RRs for women who consumed up to 5 or 15 g per day were not significantly different from 1 either. The *p*-value for trend (*p*-trend) was non-significant. The multivariate RR for 15 g or more of alcohol from wine was 1.00 (95% CI = 0.57–1.75; *p* trend = 0.95) compared to women who did not drink wine. The multivariate RR for drinking beer was 0.91 (95% CI = 0.52–1.58) and the RR for drinking liquor was 0.76 (95% CI = 0.46–1.27) compared to non-drinkers of beer and liquor, respectively. In order to evaluate possible bias because of the presence of

Table 2. Age-adjusted and multivariate RRs of ovarian cancer according to alcohol consumption in the Netherlands Cohort Study, 1986–1995

Alcohol consumption (g/day)	Age-adjusted					Multivariate[a]			
	Categorical mean (g/day)	Cases	Person years in subcohort	RR[b]	95% CI[b]	Cases	Person years in subcohort	RR[b]	95% CI[b]
Total alcohol									
No alcohol intake	0	71	6429	1	Reference	57	5766	1	Reference
0.1–4	1.9	82	7181	1.05	0.75–1.46	74	6453	1.13	0.79–1.63
5–14	9.3	38	3670	0.95	0.63–1.43	28	3377	0.85	0.53–1.37
≥15	26.3	23	2522	0.86	0.53–1.41	21	2333	0.92	0.55–1.54
				p trend = 0.54				p trend = 0.54	
Total alcohol increment per 10 g				0.99	0.83–1.17			1.01	0.84–1.21
Alcohol from wine									
No alcohol from wine	0	77	7151	1	Reference	62	6389	1	Reference
0.1–4	1.9	83	7716	1.01	0.73–1.40	75	6970	1.08	0.76–1.54
5–14	9.3	35	3091	1.06	0.70–1.62	26	2842	0.97	0.60–1.58
≥15	24.5	19	1845	0.99	0.58–1.67	17	1729	1.00	0.57–1.75
				p trend = 0.91				p trend = 0.95	
Alcohol from wine increment per 10 g				1.02	0.84–1.25			1.01	0.81–1.27
Alcohol from beer									
No		198	17,837	1	Reference	165	16,174	1	Reference
Yes		16	1966	0.76	0.45–1.30	15	1754	0.91	0.52–1.58
Alcohol from liquor									
No		194	17,200	1	Reference	162	15,548	1	Reference
Yes		20	2602	0.70	0.43–1.12	18	2380	0.76	0.46–1.27

[a] Adjusted for age (years), use of oral contraceptives (ever *versus* never), parity (number of children), height (cm), body mass index (kg/m^2), total energy intake (kcal), and current cigarette smoking (yes *versus* no).

[b] RR, rate ratio; CI, confidence interval.

subclinical disease at baseline, the data were analyzed excluding cases and subcohort members with less than one year of follow-up. These risk estimates were not substantially different (data not shown).

We also examined effect modification of the association between alcohol consumption and ovarian cancer by age at baseline, use of oral contraceptives, parity and body mass at baseline (Table 3). There was no interaction between age at baseline and alcohol consumption on the one hand and ovarian cancer risk on the other. Among women who had never used oral contraceptives, there was no association with alcohol consumption (RR = 0.99; 95% CI = 0.69–1.42), while the risk among ever users of oral contraceptives was only slightly and non-significantly increased (RR = 1.22; 95% CI = 0.51–2.91). The interaction between alcohol consumption and the number of children in terms of the risk of ovarian cancer was not consistent. The interaction with body mass index, however, appeared to show a trend. In women of normal weight (BMI < 25 kg/m^2) alcohol consumption was associated with a non-significantly increased relative risk of 1.33 (95% CI = 0.82–2.14). In overweight (BMI 25–<30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) women, alcohol consumption was associated with non-significantly decreased relative risks of 0.95 (95% CI = 0.54–1.67) and 0.52 (95% CI = 0.20–1.34), respectively. The *p*-value for interaction was 0.21. There was no interaction between energy intake and alcohol consumption on the one hand and ovarian cancer risk on the other.

Discussion

This cohort study, with a large number of cases, did not demonstrate a major association between alcohol intake

Table 3. RRs and 95% CI for ovarian cancer in women who consume alcohol compared to those NOT drinking alcohol among subgroups defined by various risk factors in the Netherlands Cohort Study, 1986–1995

Subgroup	Cases no	Subcohort person years	Drinkers[a]	
			RR[b,c]	95% CI
All	180	17,928	1.03	0.74–1.43
Age at baseline (years)				
55–59	62	7138	1.22	0.68–2.17
60–64	56	5901	0.73	0.42–1.29
65–69	62	4889	1.19	0.67–2.11
			p interaction: 0.38	
Use of oral contraceptives				
Never	150	13,287	0.99	0.69–1.42
Ever	30	4640	1.22	0.51–2.91
Parity (number of children)				
No	50	3115	1.01	0.52–1.96
1	14	1527	0.50	0.16–1.49
2	38	3980	1.98	0.89–4.41
3+	78	9307	0.90	0.56–1.46
			p interaction: 0.22	
Body mass at baseline (kg/m^2)				
Normal (<25)	98	10,098	1.33	0.82–2.14
Overweight (25–<30)	61	6286	0.95	0.54–1.67
Obese (30+)	21	1544	0.52	0.20–1.34
			p interaction: 0.21	
Energy intake (kcal/day)				
<1745	35	3527	1.07	0.53–2.17
1745–<1998	38	3562	1.86	0.83–4.19
1998–<2250	31	3563	0.51	0.24–1.05
2250–<2563	41	3547	0.94	0.46–1.92
≥2563	35	3729	1.02	0.46–2.25
			p interaction: 0.23	

[a] Compared to non-drinkers (=reference category).

[b] RR = rate ratio; 95% CI = 95% Confidence Interval.

[c] Adjusted for age (years), use of oral contraceptives (ever *versus* never), parity (number of children), height (cm), body mass index (kg/m^2), total energy intake (kcal), and current cigarette smoking (yes *versus* no).

and ovarian cancer incidence after controlling for several potential confounders among postmenopausal women. RRs for women who drank alcohol were slightly decreased compared to those for non-drinkers, but the difference was not statistically significant.

An important strength of our study is the prospective design, which makes recall bias unlikely. Bias resulting from the presence of subclinical disease at baseline is also unlikely, because an analysis excluding all cases and subcohort members with less than one year of follow-up did not change the results significantly. RRs were not significantly different. Selection bias is unlikely, given the high degree of completeness of the follow-up in terms of cases and subcohort person years [25, 35]. Another advantage is that the assessment of alcohol consumption in the NLCS allowed us to evaluate a possible association between different types of alcoholic beverage and ovarian cancer risk.

A possible limitation of our study is misclassification of alcohol consumption. The correlation between the alcohol consumption measured by the questionnaire and the measurement in a nine-day record was high, due to the large variation in alcohol consumption [26]. Also, if misclassification has occurred, this is expected to be non-differential and risk estimates are most likely biased toward no effect. Abstainers and ex-drinkers were not separated in our study, but were included in our reference category of non-drinkers. Since ex-drinkers may differ from abstainers in ovarian cancer risk, our estimated risks might be biased in either direction. The proportion of ex-drinkers is probably small, as only 4.7% of the cohort members and 2.8% of the cases who consumed less than one alcoholic drink per month reported to have drunk alcohol five years before baseline. We were able to control for confounding by the most important risk factors of ovarian cancer [29].

Of the hospital-based case–control studies that have investigated the association between alcohol and the risk of ovarian cancer (for an overview of all epidemiological studies see Table 4), two studies did not find an effect [8, 9] and five studies reported an increased risk [10–12, 19, 20]. Two of these studies observed a statistically significant trend with increasing alcohol consumption [19, 20]. One other study [18] found a protective effect of alcohol consumption, which became statistically non-significant in multivariate analysis. One other study did not find an overall effect [13], but found a protective effect of alcohol consumption in women under 50 years of age, though the effect was not statistically significant. It must be remembered, however, that hospital-based case–control studies on alcohol consumption may suffer from selection and information bias, because alcohol is linked to many diseases that require hospitalization.

Three population-based case–control studies have published results on alcohol and ovarian cancer [14, 15, 17], of which two found non-significant protective effects of alcohol consumption [14, 17] and the third a non-significantly increased risk [15]. Two cohort studies have studied the issue. In Sweden [21], the incidence of ovarian cancer at the age of 60 years and older was unaltered in alcoholic women, but the incidence under the age of 60 was 24% lower than expected in alcoholic women compared to the general population. The study design did not allow adjustment for confounding. In the Iowa Women's Health Study, a decreasing risk of ovarian cancer was observed with increasing alcohol consumption [22]. In the highest category, the RR was 0.49 after adjustment for several confounders.

Differences in the level of alcohol consumption do not explain the heterogeneity of the outcomes. The Iowa Women's Health Study [22] observed a statistically significantly decreased risk of ovarian cancer, but alcohol consumption even in the highest category was rather low (about one glass/day). The Swedish cohort study [21] was conducted among alcoholics, with a high consumption of alcohol. These women, however, probably differed in many respects from the general population, making it difficult to interpret these results. Some of the studies that observed an increased risk, although not always statistically significant, involved persons with a relatively high consumption of alcohol: more than two [11, 12] or more than three glasses per day [15, 20]. The alcohol consumption in the current study was relatively low: the highest category consisted of women who drank an average of 1.5 or more glasses of alcoholic beverage per day.

It is conceivable that both carcinogenic and protective effects of alcohol play a role in ovarian cancer. Carcinogenic effects may include an altered carcinogen metabolism [2] or alcohol-related nutritional deficiencies, *e.g.*, a lack of folate [36]. The main etiological hypotheses of ovarian cancer, *i.e.*, the 'incessant ovulation' theory of Fathalla [6] and the 'excessive gonadotropins' hypothesis of Cramer and Welch [7], indicate that suppression of ovulation and leveling of the peaks in gonadotropin levels may protect against ovarian cancer. This potential protective effect of alcohol is probably largest in the fertile period, which is in agreement with studies showing decreased risk ratios especially in younger women [13, 17, 21], but not with other studies showing increased risks in younger women [9, 20]. The current study showed a slightly increased risk in the youngest age group. It must be remembered, however, that the women were already 55–69 years of age at baseline, and the power to detect a protective effect – if any – in the youngest women of our cohort was probably too small. Based on Fathalla's

Table 4. Summary of epidemiological study findings on the relation between alcohol intake and ovarian cancer risk

Reference	Study population	Age (years)	Level of alcohol consumption	RR/OR (95% CI)[a]	*p* trend
Hospital-based case–control studies					
Williams & Horm [10]	153 cases	All	Non-drinkers	1 (reference)	–
	3035 controls		1–50 oz-years	0.74 (NS)	
			51 or more oz-years	0.85 (NS)	
Byers *et al.* [13]	274 cases	30–79	Non-drinkers	1 (reference)	NS
	1034 controls		1–8 drinks/week	0.92 (NS)	
			≥9 drinks/week	0.83 (NS)	
Tzonou *et al.* [19]	150 cases	All	Non-drinkers	1 (reference)	
	250 controls		Drinkers	1.5 (0.9–2.5)	
			Years of consumption:		
			1–9	0.7 (0.2–2.2)	0.02
			10–19	1.9 (0.7–4.8)	
			20–29	2.9 (1.1–7.6)	
			30+	1.7 (0.8–3.5)	
Mori *et al.* [8]	110 cases	All	<once/week	1 (reference)	–
	220 controls		≥once/week	1.0 (0.6–1.9)	
Hartge *et al.* [11]	296 cases	20–79	Non-drinkers	1 (reference)	0.14
	343 controls		Occasional	1.1 (0.7–1.9)	
			1–6 drinks/week	1.4 (0.8–2.3)	
			7–13 drinks/week	1.2 (0.7–2.2)	
			≥14 drinks/week	1.5 (0.8–2.8)	
Kato *et al.* [18]	417 cases	20+	None	1 (reference)	–
	8920 controls		Occasional	1.10 (0.79–1.53)	
			Daily	0.38 (0.16–0.90)	
La Vecchia *et al.* [20]	801 cases	<75	None	1 (reference)	0.04
	2114 controls		<1 drink/day	1.0 (0.7–1.4)	
			1– <2 drinks/day	1.1 (0.9–1.4)	
			2– <3 drinks/day	1.2 (1.0–1.5)	
			≥3 drinks/day	1.3 (0.9–1.8)	
Polychronopoulou *et al.* [12]	189 cases	<75	None	1 (reference)	–
	200 controls		≤1 glass/day	0.85 (0.52–1.39)	
			1–≤2 glasses/day	0.94 (0.49–1.79)	
			>2 glasses/day	1.62 (0.66–3.96)	
Nandakumar *et al.* [16]	97 cases	48.3[c]	History of alcohol consumption:		–
	194 controls		No	1 (reference)	
			Yes	1.3 (0.2–8.0)	
Tavani *et al.* [9]	1031 cases	<80	Never drinkers	1 (reference)	0.41
	2411 controls		<12 g/day	1.02 (0.80–1.30)	
			>12–24 g/day	1.29 (1.00–1.67)	
			>24–36 g/day	1.04 (0.80–1.36)	
			≥36 g/day	1.09 (0.76–1.57)	
Population-based case–control studies					
Gwinn *et al.* [17]	433 cases	20–54	None	1 (reference)	–
	2915 controls		<50 g/week	1.0 (0.7–1.4)	
			50–149 g/week	0.8 (0.5–1.1)	
			150–249 g/week	1.0 (0.6–1.6)	
			≥250 g/week	0.5 (0.2–0.9)	
Whittemore *et al.* [14]	188 cases	18–74	None	1 (reference)	–
	539 controls		≥20 drinks/week	0.66 ($p = 0.34$)	
Kuper *et al.* [15]	549 cases		None	1 (reference)	0.20
	516 controls		0–1 drinks/day	0.91 (0.67–1.23)	
			>1–2 drinks/day	1.33 (0.88–2.01)	
			>2–3 drinks/day	0.92 (0.50–1.69)	
			>3 drinks/day	1.35 (0.80–2.26)	
Cohort studies					
Kushi *et al.* [22]	29,083 subjects	55–69[b]	None	1 (reference)	0.01
	139 cases		0.9–3.9 g/day	1.37 (0.39–2.04)	

Table 4. (Continued)

Reference	Study population	Age (years)	Level of alcohol consumption	RR/OR (95% CI)[a]	*p* trend
			4–<10 g/day	0.61 (0.28–1.34)	
			≥10 g/day	0.49 (0.24–1.01)	
Lagiou *et al*. [21]	36,856 subjects	42.7[b,c]	General population	1 (reference)	–
	76 cases		Alcoholics	0.86 (0.68–1.08)	
Schouten *et al*. (current study)	214 cases	55–69[b]	None	1 (reference)	0.54
			<5 g/day	1.13 (0.79–1.63)	
			5–14 g/day	0.85 (0.53–1.37)	
			≥15 g/day	0.92 (0.55–1.54)	

[a] RR = Risk ratio; OR = Odds ratio; 95% CI = 95% Confidence intervals; reference = reference category; NS = non-significant.
[b] Age at enrollment.
[c] Mean age.

theory, one might also expect that, because of the similarity of the proposed mechanisms of protection, alcohol would not provide additional protection against ovarian cancer in women who used oral contraceptives, as ovulation is already suppressed in these women. In the current study, women who used oral contraceptives and consumed alcohol had a slightly but not statistically significantly increased risk of ovarian cancer compared to women who did not consume alcohol. Two other case–control studies have studied the interaction between the use of oral contraceptives and alcohol intake. Both studies observed a non-significant protective effect of alcohol intake in women who had ever used oral contraceptives [9, 20].

An interesting finding in the current study was the decreased – although not statistically significantly decreased – risk of ovarian cancer in overweight and obese women who consumed alcohol. This was not confirmed in the only case–control study that investigated this interaction [9]. In view of the possibility of a chance finding, confirmation of this result in other studies is needed. Tavani [9] observed a protective effect of alcohol intake among women with a low energy intake. This was not confirmed in the current study.

In conclusion, alcohol intake was not associated with ovarian cancer risk in our cohort study. We cannot exclude that alcohol intake protects against ovarian cancer occurring at younger age, because the women in our cohort were already too old at baseline to demonstrate or refute this effect. Future studies on alcohol intake should focus on younger cohorts and should investigate a possible interaction with oral contraceptives and body mass index.

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